UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,049	05/05/2008	Jeffrey W. Strovel	689290-275	4653

27162 7590 09/21/2010

CARELLA, BYRNE, CECCHI, OLSTEIN, BRODY & AGNELLO
5 BECKER FARM ROAD
ROSELAND, NJ 07068

EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
09/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,049	STROVEL ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-9,12-27 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,48-55 and 57-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group IV in the reply filed on July 15, 2010 is acknowledged. The traversal is on the ground(s) that a change in expression of a gene is likely to produce a change in the encoded protein level and likely to be determined by a search in the art. This is not found persuasive because an increase or decrease in protein levels does not necessarily correlate to an increase or decrease in mRNA levels and there is no showing in the present specification and no evidence has been provided to establish that level of protein encoded by SEQ ID NO: 80 is increased or decreased in cancer cells in a manner consistent with the level of the mRNA encoded by SEQ ID NO: 80. Further, the search for methods of detecting cancer cells by detecting a protein is not commensurate in scope with the search for methods of detecting cancer cells by detecting a mRNA, and therefore it is maintained that undue burden would be required to examine invention V with the elected invention of Group IV.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-9, 12-47 and 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 15, 2010.

Claim Objections

3. Claims 10, 11, 48-55 and 57-60 are objected to because the claims encompass the subject matter of the non-elected inventions of methods which detect expression of

SEQ ID NO: 80 by assaying for protein levels and methods which assay for the expression of the non-elected nucleic acids of SEQ ID NO: 1-79 and 81-3049.

4. Applicant is advised that should claims 57 and 58 be found allowable, claims 59 and 60 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10, 11, 48-55 and 57-60 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Based upon consideration of all of the relevant factors with respect to the claim as a whole, claims 10, 11, 48-55 and 57-60 are held to claim an abstract idea, and is/are therefore rejected as ineligible subject matter under 35 U.S.C. 101. The rationale for this finding is explained below:

Claims 10 and 11 are drawn to methods for detecting a cancerous status of a cell comprising detecting elevated expression in a cell of SEQ ID NO: 80. Detection of elevated expression of SEQ ID NO: 80 can be accomplished by reading a document or information in a database regarding the expression level of SEQ ID NO: 80. Detecting does not require performing a step that is transformative. The claims encompass an

abstract idea and involve performing only a mental step. Similarly, claims 48-51 encompass methods that monitor in a patient undergoing therapy, the expression of a gene. Claims 52-55 also require only monitoring gene expression in a patient undergoing therapy, wherein a decrease in expression is indicative of the likelihood of success of therapy. Claims 48-55 do not set forth how expression is monitored. Thus, the claims encompass monitoring expression by reading a document or database to determine the expression level of a gene. Accordingly, claims 48-55 are also considered to include only a mental step. Claims 57-60 are directed to a method for determining the progress of treatment for cancer comprising determining a change in expression of SEQ ID NO: 80 during the course of treatment as compared to prior to treatment. The claims do not set forth how the determining step is accomplished. Accordingly, the claims encompass performing only the mental step of reading a printout out or information in a database to determine a change in expression levels.

The unpatentability of abstract ideas was confirmed by the U.S. Supreme court in Bilski v. Kappos, No. 08-964, 2010 WL 2555192 (June 28, 2010). Factors weighing toward patent eligibility include: (i) a recitation of a machine or transformation wherein the Machine or transformation is particular, the machine or transformation meaningfully limits the execution of the steps, the machine implements the claimed steps, the article being transformed is particular, the article undergoes a change in state or thing (e.g., objectively different function or use), the article being transformed is an object or substance; (ii) a claim directed to applying a law of nature, wherein the law of nature is practically applied and the application meaningfully limits the execution of the steps; and

(iii) the claim is more than a mere statement of a concept, such that the claim describes a particular solution to a problem to be resolved, implements a concept in some tangible way, and the performance of steps is observable and verifiable.

In the present situation, the claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing. Nor do the claims directly apply a law of nature in a practical manner with meaningful execution steps or implement more than a concept by performing observable and verifiable steps. In particular, the claims do not require the transformation of an article or physical object to a different state. Transformation of data is not considered a physical transformation. Moreover, the claims do not recite the application of a law of nature and meaningfully limit the execution steps. Nor do the claims describe a particular solution to a problem to be solved and implement the concept in a tangible way, particularly by performing steps that are observable and verifiable.

It is noted that the claims may be drawn to statutory subject matter if the claimed methods were amended so that the preamble of the claim is clearly connected to the body of the claim and to specifically require active process steps – e.g.., a method for detecting a cell that is cancerous based on the detection of an increase level of expression of a polynucleotide comprising SEQ ID NO: 80 comprising active process steps such as obtaining a cell from a patient, contacting the cell with a polynucleotide probe comprising SEQ ID NO: 80 to form a hybridization product between the polynucleotide probe and target nucleic acids in the cell, determining the quantity of said

hybridization product to thereby determine the level of expression of the polynucleotide comprising SEQ ID NO: 80 in the cell, wherein an elevated level of expression of the polynucleotide comprising SEQ ID NO: 80 in the cell, as compared to a control cell, indicates that the cell is cancerous.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 11, 48-55 and 57-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 11, 52-55 and 57-60 are indefinite over the recitation of "gene corresponding to a polynucleotide" (claim 10, lines 2-3; claim 52, line 3; claim 57, line 5). Corresponding is not an art recognized term to describe the relationship between two nucleic acid sequences. It is not clear as to whether a corresponding polynucleotide is the same as the gene, shares an unstated level of sequence identity with the gene, encodes for a protein with a similar function, is a homologue of the gene, etc. Because the term "corresponding" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to nucleic acid sequences, one of skill in the art cannot determine the meets and bounds of the claimed subject matter. Similarly, claims 48-51 are indefinite over the recitation of "gene corresponding to a polypeptide" (claim 48, line 3) because neither the specification nor the claims define what is intended to be meant by a gene corresponding to a

polypeptide and there is no art recognized definition for corresponding as it relates to genes and polypeptides.

Claims 10 and 11 are indefinite over the recitation of “elevated expression." The term "elevated" in claims 10 and 11 is a relative term which renders the claims indefinite. The term "elevated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, the claims do not set forth what the elevated expression is relative to (another cancer cell, a normal cell etc) and thereby it is unclear as to what would constitute an elevated expression.

Claims 48-51 are indefinite. The claims are drawn to a method for monitoring the progress of cancer therapy. The claims recite only a single step of monitoring expression of SEQ ID NO: 80. The claims do not, however, recite an active process of monitoring the progress of cancer therapy per se. The claims do not clarify how monitoring expression is equivalent to or results in monitoring cancer therapy. It is thereby unclear as to whether the claims are intended to be limited to a method which only determines the expression of SEQ ID NO: 80 during the course of therapy or if the claims are intended to be limited to methods which monitor the progress of cancer therapy. In the later case, the claims omit the essential process step of monitoring the progress of cancer therapy. See MPEP § 2172.01. Note that MPEP 2773.02 states that if the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid

infringement, a rejection of the claim under 35 USC 112, second paragraph, is appropriate.

Claims 48-51 are indefinite over the recitation of “gene corresponding to a polypeptide having a sequence" of SEQ ID NO: 80. SEQ ID NO: 80 is a nucleotide sequence, rather than a polypeptide sequence. Accordingly, it is unclear as to what is intended to be meant by a polypeptide having a sequence of SEQ ID NO: 80.

Claims 52-55 are indefinite over the recitation of “decrease in said expression." The term "decrease" in claim 52 is a relative term which renders the claim indefinite. The term "decrease" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, the claims do not set forth what the decrease in expression is relative to and thereby it is unclear as to what would constitute a decrease in expression.

Claims 57-60 are indefinite over the recitation of “determining in said patient a change in expression" (claims 57 and 59, step a) because it is unclear as to what constitutes a change in expression since the claim does not indicate what the expression is being compared to (i.e., a change as compared to what?). Further, claims 59 and 60 are indefinite over the recitation of “said change” (claims 57 and 59, line 10 and claims 58 and 60, line 1) because it is unclear as to whether “said change” refers to the change detected in step (a), or the change detected in step (b), or the changes detected in both steps (a) and (b).

Claim Rejections - 35 USC § 112 first paragraph - Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 11, 48-55 and 57-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for detecting the cancerous state of a cell and for monitoring the progress of cancer therapy comprising detecting an elevated level of expression or a change in the level of expression of a polynucleotide corresponding to a polynucleotide or polypeptide sequence of SEQ ID NO: 80.

The claims encompass the detection of a significantly large genus of possible polynucleotides as indicative of the presence of a cancer cell or as a means to monitor cancer therapy. The claims recite the language of detecting expression of a “gene

corresponding to a polynucleotide comprising a sequence" of SEQ ID NO: 80 (claims 10, 11, 52-55 and 57-60) and "a gene corresponding a polypeptide comprising a sequence of" SEQ ID NO: 80 (claims 48-51). As discussed above, the term "corresponding" is not defined in the specification or claims and there is no art recognized definition for this phrase as it relates to the relationship between polynucleotides or polynucleotides and polypeptides. Accordingly, the phrase has been given it's broadest reasonable interpretation as including genes that share any level of sequence identity or complementarity (e.g. 50% or 30% etc) with SEQ ID NO: 80, genes that are homologues of the gene encoding the cDNA of SEQ ID NO: 80, and genes which encode for proteins that share some unspecified functional properties with a protein encoded by SEQ ID NO: 80. In view of the "a sequence of SEQ ID NO: 80" language, the claims encompass genes that correspond to a polynucleotide that comprises only a portion (100 or 50 or 1 nucleotides) of SEQ ID NO: 80. Thus, the claims encompass detecting expression of essentially any gene as indicative of the cancerous state of a cell or the success of cancer therapy.

Claims 10 and 11 recite detecting elevated expression in a cell. The claims do not require that the cell is isolated from a patient and thus include methods wherein the cell is provided in vivo and the amount of RNA is measured in vivo. Claims 48-55 recite "monitoring in a patient undergoing cancer therapy the expression of a gene." Claims 57-60 recite "determining in said patient a change in expression." Accordingly, claims 48-55 and 57-60 also encompass methods of analyzing gene expression levels in vivo.

Claims 10 and 11 do not recite the source of the cell. Claims 48-55 and s57-60 recite monitoring expression in a patient. The term “patient” is not defined in the specification or claims and thereby has been given its broadest reasonable interpretation as including a human or non-human patient. Accordingly, the claims broadly encompass detecting the cancerous state of a cell and monitoring cancer treatment by assaying cells and other samples obtained from such diverse non-human subjects as dogs, horses, monkeys, rats, pigs rabbits etc.

Claims 51, 55 and 60 are directed to methods wherein the cancer is any cancer of the breast, colon, lung or prostate tissue. Claims 10, 11, 48-50, 52-54 and 57-59 encompass detecting any type of cancerous cell or monitoring therapy for any type of cancer, including such diverse cancers as skin cancer, brain cancer, leukemia, renal cancer etc.

The claims also include analyzing cells and nucleic acid samples obtained from any source – e.g., skin cells, saliva, ascites fluid, urine, feces etc – for the expression level of SEQ ID NO: 80.

Nature of the Invention

The claims encompass methods for detecting the cancerous state of a cell and for monitoring cancer therapy by assaying for the level of gene expression. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification discloses 3,049 cDNAs present in amplicons that were detected in cancer cell lines. The specification (page 12) states that:

> In addition, SEQ ID NO: 1-3049 represents the nucleotide sequences for cDNA sequences corresponding to genes located in these regions of interest. Such regions contain genes found to be amplified and over-expressed in cancerous tissues, especially of breast, colon, lung, cervix, kidney, pancreas and prostate.
>
> Each amplicon may contain about 75 genes, at least one of which will be amplified in a cancerous condition. Genes that show amplification and/or over-expression can be indicative of the cancerous status of a given cell.

In Table 1, the specification lists 11 amplicons (i.e., Amplicon A1-A11), the chromosome on which they were found, the number of the first and last nucleotide number of the amplicon and the length of the amplicon.

The specification (page 10) characterizes Table 2 as listing " tissues where the amplicons are found, cell lines expressing them, the amplification ratios found in those tissues for cancer versus normal cells, amplicon size and the chromosomal locations of the amplicons.

The elected polynucleotide of SEQ ID NO: 80 is the cDNA for "ENST00000261573." In Table 3, "ENST00000261573" is characterized as the STK24 gene, present on chromosome 13 and also present in amplicon A2. The start and stop site for STK24 is listed as 96803428 and 96872017, respectively.

As recited in Table 2, amplicon A2 appears to be present in 5 breast cancer cell lines and 2 lung cancer cell lines.

The specification also teaches methods that can be performed to determine the level of expression of a gene in a cancer cell (see, e.g., para [0145-0146]).

Additionally, the prior art of Mack et al (PGPUB 2004/0005563) teaches that STK24 is expressed at an elevated level in ovarian cancer cells as compared to normal ovarian cells (Table 15A). However, the present specification does not specifically contemplate methods which detect an elevated expression of the STK24 gene as indicative of an ovarian cancer cell or methods for monitoring expression of STK24 in samples from a patient undergoing treatment for ovarian cancer. Accordingly, the specification cannot be relied upon for providing support or enablement for methods for detecting ovarian cancer by assaying by assaying for expression of STK24 or methods for monitoring the progress of therapy or determining the likelihood of success of therapy for ovarian cancer by assaying for expression of STK24, as taught by Mack.

Further, Jiang et al (PGPUB 2003/0087818) teaches methods for detecting a colon cancer and methods for diagnosing colon cancer by assaying for an increase in expression of the clone "R0636: B04_Homo," comprising a cDNA referred to therein as SEQ ID NO: 1359 (para [1110]). This sequence shares 100% identity with the inverse complement of nucleotides 475-948 of present SEQ ID NO: 80 (see para 9 below). However, the present specification does not specifically contemplate assaying for colon cancer by detecting the expression of the sequence of SEQ ID NO: 1359 of Jiang. Thereby, the specification cannot be relied upon for providing support or enablement for methods of detecting colon cancer or methods for monitoring the progress of therapy for colon cancer or determining the likelihood of success of colon cancer therapy by assaying for expression of SEQ ID NO: 1359, as taught by Jiang.

The Predictability or Unpredictability of the Art :

The art of determining an association between chromosomal alterations, such as copy number, and gene expression levels and the occurrence of a phenotype, such as cancer, is highly unpredictable. There are a significantly large number of alterations that may occur in chromosomal sequences, wherein the alterations may comprise the deletion of one or more nucleotides or the addition or substitution of one or more nucleotides or the rearrangement of genes or gene fragments. It is highly unpredictable as to which of the vast number of possible alterations that occur in the genome may be correlated with the occurrence of a particular cancer. Further, gene expression may be influenced by a number of factors, in addition to disease itself, and these factors must be considered prior to drawing any conclusions regarding an association between gene expression patterns and prognostic factors associated with cancer, such as the occurrence of cancer, the outcome of cancer, or the response to treatment for cancer. Thereby, it is highly unpredictable as to which of the enormous number of different genes present in an amplified will be indicative of cancer, or progression of cancer, and/or whether the expression level of individual genes present in an amplicon will be indicative of cancer or progression of cancer.

In the present situation, the specification does not appear to specifically teach that the amplicons are detected in primary breast or lung cancer, and are not detected in primary normal breast. Rather, Table 2 appears to list only cell lines in which the chromosomal regions are amplified. It is well accepted that the genetic alterations which occur in cell lines are not necessarily reflective of the genetic changes which occur *in vivo*. For instance, Dermer, G.B. (Bio/Technology (1994) 12: 320) states that

"The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body." Dermer concludes that "Petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." Since the results obtained in vitro in cell lines cannot be extrapolated to in vivo, knowledge that a chromosomal region containing a gene is amplified in a cell line as compared to a control cell line does not allow one to conclude that this chromosomal region or gene is amplified and it's expression level is elevated in primary or metastatic cancer *in vivo*.

Moreover, the specification (page 12) teaches that up to 75 different genes may be present in each amplicon. However, the specification does not teach that amplification of the gene encoding the cDNA of SEQ ID NO: 80 alone is sufficient to indicate the occurrence of cancer, or that loss of amplification of this gene is indicative of the success of cancer therapy or absence of progression of cancer.

The specification does not provide any data regarding the actual level of expression of the polynucleotide of SEQ ID NO: 80 in breast or lung or prostate or colon cancer cells or in any other type of cancer cell. It is highly unpredictable as to whether an elevated expression of SEQ ID NO: 80 occurs in one or more or all types of cancer cells in the absence of evidence establishing such a finding.

The prior art and post-filing date art support the finding that a change in copy number is not necessarily predictive of a change in gene expression levels.

For example, Henrich (Clinical Cancer Research. 01 January 2006. 12: 131-138). Henrich teaches that the 1p36.3 region is frequently deleted in neuroblastomas. This

region includes the genes FLJ10737 and CAMTA1. However, Henrich did not find any evidence of a decrease in expression of FlJ10737 in subjects having the 1p deletion (see abstract and page 135). Expression levels of FLJ10737 were not correlated with variables of poor outcome such as MYCN amplification or advanced stages of cancer (page 135). Accordingly, the fact that a gene is present in a chromosomal region deleted in cancer is not predictive of the expression levels of that gene or a correlation between expression levels of the gene and prognostic variables related to cancer.

Similarly, Sutherland et al (Acta Oncologica. 1995. 34: 651-656) teaches that while cyclin D1 gene amplification was detected in six cell lines, amplification was not a prerequisite for and did not always lead to increased cyclin D1 expression (page 654, second col.).

Further, the present claims are inclusive of methods in which a cancer cell is detected or the progress of cancer or cancer therapy is monitored in any non-human subject. The specification appears to provide the results of only a study regarding amplification of chromosome 13 sequences in human cancer cell lines. The specification does not teach the amplification of amplicon A2, or the amplification of the gene encoding the cDNA of SEQ ID NO: 80, or the elevated expression of SEQ ID NO: 80 in a representative number of non-human organisms

The art of extrapolating expression profiling results from one animal to other animals is highly unpredictable. The prior art corroborates this unpredictability. For example, Liu et al (Clinical Immunology. 2004. 112: 225-230) studied gene expression in T lymphocytes in human autoimmune disease and murine models of autoimmune

disease, including SLE. Liu (see abstract) reported that "we found very little overlap in the gene expression profile between human autoimmune disease and murine models of autoimmune disease and between different murine autoimmune models." Only 2 out of 129 genes differentially expressed in human SLE were also found to be differentially expressed in animal models of SLE/autoimmune disease (see page 228).

Coleman (Drug Discovery Today. 2003. 8: 233-235) found that gene expression patterns between mice and humans shared some degree of similarity, but that the basic patterns of gene expression differed and that there was no general rule for predicting gene expression (page 234). Coleman concluded that '(t)he validity of mouse or other animal species as a human surrogate should not be assumed." These teachings of Coleman support the finding that there is no predictable means for determining whether the gene expression profile obtained in a human will be identical to that in the diverse genus of mammals encompassed by the claims.

Similarly, Saetre (Molecular Brain Research. 2004. 126: 198-206) teaches that there is significant variation in gene expression between species, and even between closely related species. Saetre studied gene expression patterns in the brains of domestic dogs, gray wolves and coyotes and identified 114 genes with strong evidence for differential inter-species expression (page 201 and 203, col. 2).

The present claims further include analyzing any type of biological sample for the presence of an elevated level of expression or a change in level of expression of a polynucleotide comprising SEQ ID NO: 80, whereas the present specification provides results obtained using from breast and lung cancer cell lines. It is unpredictable as to

what other types of body fluids and tissues may be monitored for expression of a gene encoding SEQ ID NO: 80 in order to monitor cancer therapy or the progress of cancer. Modification of gene expression most frequently occurs in only a subset of cells that are directly involved in a disease such as cancer. The levels of particular mRNAs are well known to vary significantly between different cell, tissue and fluid types. Given that gene expression is often cell-type or tissue-type specific and that changes in gene expression patterns associated with a disease, such as cancer, are often variable between the particular tissue types that are affected by the disease, the identity of particular genes whose expression is increased or decreased is expected to be different for different cell, tissue and body fluid types.

The fact that gene expression may vary significantly between tissue types is well accepted in the art. For example, Saetre identified 156 genes which showed region-specific expression patterns in the brains of domestic dog, gray wolf and coyote (page 200). Saetre (page 204) also notes that other studies have identified significant differences in gene expression between four regions of the brain in mice, as well as differences in expression patterns between strains of mice. Thus, one cannot determine a priori which cells or other types of biological samples will show a change in the level of expression as indicative of cancer progression or response to cancer therapy.

As discussed above, in view of the "corresponding" and "a nucleotide sequence" language, the claims encompass detecting expression of a wide array of polynucleotides that are not well characterized in terms of any signficant identifying features, such as their complete structure, their location in the genome (i.e.,

chromosome or chromosomal band), the protein they encode or the function of the protein they encode etc. It is highly unpredictable as to what would be the identity of such genes that correspond to a nucleotide sequence or portion thereof of SEQ ID NO: 80, and as to which, if any, of such genes show an increase level of expression in breast or lung, or prostate or colon or any other cancer.

Even if the specification establishes that the mRNA encoded by the polynucleotide of SEQ ID NO: 80 is present at increased levels in breast and lung cancer, it is highly unpredictable as to whether a similar increase in the level of mRNA encoded by SEQ ID NO: 80 would be indicative of a representative number of other types of cancer. Note again that the specification does not in fact provide any data establishing that SEQ ID NO: 80 is present at elevated levels in primary breast or lung cancer cells, as compared to normal breast and lung cancer cells. There is no showing that a representative number of different types of cancers show an increase or decrease in the level of mRNA encoded by SEQ ID NO: 80. The unpredictability of extrapolating any findings disclosed in the specifcation with breast or lung cancer to any type of cancer is compounded by the fact that neither the specification nor the prior art teach a clear structure-function relationship between the cDNA of SEQ ID NO: 80 and cancer.

The unpredictability of extrapolating the findings concerning changes in the level of expression associated with one type of cancer to other types of cancer is supported by the teachings of Schmidt (Blood. 1998. 91: 22-29). Schmidt found that while ICSBP mRNA levels were decreased in CML, AML and ALL leukemias, ICSBP mRNA levels were not correlated with NB, CLL or CMMoL leukemias (Table 1 and page 24). Thus,

Schmidt evidences the fact that expression results obtained with one type of cancer cannot be predictably extrapolated to other types of cancer.

Moreover, as discussed above, the claims appear to encompass methods wherein cell is provided in vivo and the amount of mRNA is measured in vivo as indicative of the cancerous status of the cell or in order to monitor the progress of cancer or the outcome of cancer therapy. However, the specification does not teach any particular methodologies which could be used to measure the level of mRNA expressed from a gene comprising SEQ ID NO: 80 in vivo. To perform such methodology in vivo is highly unpredictable. A large number of factors must be overcome in order to perform such methods including the selection of the route of administration of an agent that would hybridize to and detect target nucleic acids,, the type of cells that must be targeted, and the conditions under which the agent would be administered. The administration of a nucleic acids and other types of chemical detection agents requires that the molecules are also protected from degradation or sequestered from immune attack in order for those molecules to reach the appropriate skin cells. However, the specification does not provide any of the necessary guidance required to overcome the problems recognized in the art with respect to the systemic delivery of a polynucleotide probe or other agent that detects the level of mRNA or genomic DNA in a cell. The additional experimentation required to practice such a method is not routine and would amount to significant advancement above the state of the art at the time of filing. As such, the additional experimentation is considered undue.

Quantity of Experimentation and Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify additional genes "corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 80" that can be used to detect the cancerous state of a cell, monitor cancer therapy or determine the progress of cancer. There is no information provided regarding a particular structure-function relationship between SEQ ID NO: 80 and cancer so that one could determine a priori that expression of a particular gene sharing sequence identity with SEQ ID NO: 80 or encoding a protein having a similar function to that of the protein encoded by SEQ ID NO: 80 would be correlated with cancer. The specification also does not provide any specific guidance as to the identity of additional genes related to SEQ ID NO: 80 whose expression is correlated cancer.

The specification also does not provide sufficient guidance as to how to predictably extrapolate findings obtained in human subjects to non-human subjects, how to predictably extrapolate the findings obtained in a particular cancer type (breast or lung cancer) to a representative number of other cancers, or how to predictably extrapolate the findings obtained in particular cell types (breast or lung) to a representative number of other cell types or other types of biological samples (serum, feces, urine, etc).

In the present situation, extensive experimentation would be required to establish if the expression of the polynucleotide of SEQ ID NO: 80 is correlated with breast or

lung cancer or other cancers in human and non-human patients. Extensive experimentation would also be required to identify additional genes in the genome of human or non-human patient's whose increase or decrease in expression in a cell or other type of biological sample is predictive of breast or lung cancer or any other cancer.

35 USC 112 first paragraph requires that the invention is enabled at the time the invention is made. "[T]o be enabling, the specification.., must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Wright, 999 F.2d at 1561, 27 USPQ2d at 1513 (emphasis added), quoted in Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2 1001, 1004 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." In re Vaeck, 947 F.2d 488, 496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), quoted in Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138 (Fed. Cir. 1999).

Thus, while methods for expression profiling are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for mRNAs whose expression patterns may linked to the occurrence of breast or lung cancer or other cancers. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for detecting the cancerous state of

a cell or monitoring cancer therapy or progression of cancer by assaying for the expression of a gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 80.

Working Examples

The specification exemplifies methods of detecting amplification of an amplicon "A2" in human breast and lung cancer cell lines.

The specification does not provide any working examples of detecting the cancerous state of a cell by detecting an elevated level of expression of gene that encodes the cDNA of SEQ ID NO: 80, or methods for monitoring the progress of cancer therapy or the success of cancer therapy treatment by assaying for a change in the level of expression of a gene that encodes the cDNA of SEQ I D NO: 80.

The specification does not provide any working examples in which a cancer cell is detected or cancer therapy is monitored in vivo by assaying for expression of a gene that encodes the cDNA of SEQ ID NO: 80.

No working examples are provided wherein a cancer cell is detected or cancer therapy is monitored in a non-human subject by detecting elevated expression or a change in the level of expression of SEQ ID NO: 80.

No working examples are provided of genes that "correspond to a polynucleotide comprising a nucleotide sequence of" SEQ ID NO: 80, or the detection of expression of such genes to detect the cancerous state of a cell or monitor cancer therapy in a patient.

No working examples in which gene expression levels of SEQ ID NO: 80 are determined in any type of biological sample (e.g., serum/plasma, blood, feces, urine), other than a cancer cell and particularly a breast or lung cancer cell line, and the gene expression levels are used to detect the cancerous status of a cell or monitor cancer therapy.

Conclusions:

As set forth in Rasmusson v. SmithKline Beecham Co~., 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

"As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Moreover, case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of

knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the present situation, Applicants have established only that amplicons containing the STK24 gene having the cDNA of SEQ ID NO: 80 are amplified in breast and lung cancer cell lines. The specification has not established that the STK24 gene encoding the cDNA of SEQ ID NO: 80 is expressed at higher levels in breast or lung cancer cells, as compared to primary cells. The specification teaches only how to perform assays to try to determine if the levels of mRNA encoded by SEQ ID NO: 80 are elevated in cancer cells. The specification does not teach the outcome of such assays and does not teach one of skill of the art how to practice the claimed invention without undue experimentation.

Additionally, the claims do not bear a reasonable correlation to the scope of enablement because the specification identifies amplification of the chromosome 13 region containing the STK24 gene only in human breast and lung cancer cell lines, whereas the claims encompass detecting any type of cancer cell or monitoring therapy of any type of cancer in a human or in any non-human subject. Further, the teachings in the specification are limited to the human cDNA of SEQ ID NO: 80, whereas the claims encompass detecting expression of a vast genus of genes, that have not been clearly described in terms of their chemical structure or function in the claims or specification and which have not been established as showing an elevated level of expression in a

representative number of cancers. In view of the unpredictability in the art, and the lack of disclosure and guidance provided in the specification and in the prior art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 10, 11, 48-50, 52-54 and 56-60 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Mack et al (PGPUB 2004/0005563).

Mack teaches methods for detecting an ovarian cell (i.e., detecting the cancerous state of a cell) comprising detecting elevated expression of serine/threonine kinase 24 (STK24; i.e., a gene 'corresponding' to a polynucleotide comprising SEQ ID NO: 80; see Table 15A, para [0012]). Mack teaches that STK24 is expressed at an elevated level in ovarian cancer cells as compared to normal ovarian cells (Table 15A). Thereby, Mack teaches that detection of elevated expression of STK24 in an ovarian cell is indicative of the presence of a cancerous ovarian cell.

Regarding claim 11, this claim recites only that "elevated expression is an elevated copy number of the gene." The claim does not require detecting an elevated copy number. Thus, claim 11 does not recite any limitations that distinguish the claimed method over the method of Mack which detects elevated expression of the STK24 gene.

Regarding claims 48-50, 52-54 and 56-50, Mack further teaches a method for monitoring treatment of a patient with ovarian cancer comprising administering a cancer treatment to the patient and determining the gene expression level of the STK24 gene (see, e.g., para [0012] and [0024-0025]). Further, regarding claims 52-54 and 56-60, Mack teaches methods for evaluating and confirming diagnosis and treatment outcomes comprising comparing the level of expression in a sample from the patient after treatment with a sample from the patient prior to treatment, wherein a change (decrease) in the level of expression of STK24 is detected and indicates progress of treatment and success of treatment (para [0024-0025], [0105-016]). Regarding claims 50 and 54, Mack teaches that the treatment regimen to be evaluated may be chemotherapy (para [0106]).

9. Claims 10 and 11 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Jiang et al (PGPUB 2003/0087818).

Jiang teaches the identification of a clone "R0636: B04_Homo," comprising a cDNA referred to therein as SEQ ID NO: 1359 (para [1110]). The cDNA of SEQ ID NO: 1359 was identified as being over-expressed at at least a 2-fold level in colon cancer cells as compared to normal colon cells (para [1474] and Table 14). Jiang teaches

methods for detecting a colon cancer and methods for diagnosing colon cancer by assaying for an increase in expression of SEQ ID NO: 1359 (e.g., para [1408-1409] and [1430]).

SEQ ID NO: 1359 was compared to sequences in the GenBank Database and is described as having sequence similarity with the human serine/threonine kinase 24 (STK24) gene. SEQ ID NO: 1359 of Jiang consists of 478bp. This sequence shares 100% identity with the inverse complement of nucleotides 475-948 of present SEQ ID NO: 80 ("query" below):

```
Query  475  GCGGCCAACGTCCTGCTGTCTGAGCATGGCGAGGTGAAGCTGGCGGACTTTGGCGTGGCT  534
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  478  GCGGCCAACGTCCTGCTGTCTGAGCATGGCGAGGTGAAGCTGGCGGACTTTGGCGTGGCT  419

Query  535  GGCCAGCTGACAGACACCCAGATCAAAAGGAACACCTTCGTGGGCACCCCATTCTGGATG  594
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  418  GGCCAGCTGACAGACACCCAGATCAAAAGGAACACCTTCGTGGGCACCCCATTCTGGATG  359

Query  595  GCACCCGAGGTCATCAAACAGTCGGCCTATGACTCGAAGGCAGACATCTGGTCCCTGGGC  654
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  358  GCACCCGAGGTCATCAAACAGTCGGCCTATGACTCGAAGGCAGACATCTGGTCCCTGGGC  299

Query  655  ATAACAGCTATTGAACTTGCAAGAGGGGAACCACCTCATTCCGAGCTGCACCCCATGAAA  714
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  298  ATAACAGCTATTGAACTTGCAAGAGGGGAACCACCTCATTCCGAGCTGCACCCCATGAAA  239

Query  715  GTTTTATTCCTCATTCCAAAGAACAACCCACCGACGTTGGAAGGAAACTACAGTAAACCC  774
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  238  GTTTTATTCCTCATTCCAAAGAACAACCCACCGACGTTGGAAGGAAACTACAGTAAACCC  179

Query  775  CTCAAGGAGTTTGTGGAGGCCTGTTTGAATAAGGAGCCGAGCTTTAGACCCACTGCTAAG  834
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  178  CTCAAGGAGTTTGTGGAGGCCTGTTTGAATAAGGAGCCGAGCTTTAGACCCACTGCTAAG  119

Query  835  GAGTTATTGAAGCACAAGTTTATACTACGCAATGCAAAGAAAACTTCCTACTTGACCGAG  894
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  118  GAGTTATTGAAGCACAAGTTTATACTACGCAATGCAAAGAAAACTTCCTACTTGACCGAG  59

Query  895  CTCATCGACAGGTACAAGAGATGGAAGGCCGAGCAGAGCCATGACGACTCGAGC  948
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  58   CTCATCGACAGGTACAAGAGATGGAAGGCCGAGCAGAGCCATGACGACTCGAGC  5
```

In view of the sequence identity shared between SEQ ID NO: 1359 of Jiang and present SEQ ID NO: 80, the gene encoding the cDNA of SEQ ID NO: 1359 is considered to be a gene corresponding to a nucleotide sequence of SEQ ID NO: 80. Note that the term “corresponding” is not clearly defined in the claims or specification and there is no art recognized definition for this term as it relates to nucleic acids. Thereby, the term "corresponding” has been given its broadest reasonable interpretation as including polynucleotides that show sequence similarity to SEQ ID NO: 80 and portions thereof. Accordingly, Jiang is considered to teach a method for detecting the cancerous status of a cell (i.e., detecting a colon cancer cell) comprising detecting elevated expression of a gene corresponding to a polynucleotide comprising SEQ ID NO: 80 (i.e., expression of the cDNA of SEQ ID NO: 1359 of Jiang).

Regarding claim 11, this claim recites only that “elevated expression is an elevated copy number of the gene.” The claim does not require detecting an elevated copy number. Thus, claim 11 does not recite any limitations that distinguish the claimed method over the method of Jiang which detects elevated expression of the cDNA of SEQ ID NO: 1359 therein having sequence identity with the STK24 gene.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 48-55 and 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang (PGPUB 2003/0087818).in view of Mack (PGPUB 2004/0005563).

The teachings of Jiang are presented above. In summary, Jiang teaches detecting colon cancer by detecting elevated expression of a gene corresponding to a polynucleotide sequence of present SEQ ID NO :80 (i.e., expression of the polynucleotide of SEQ ID NO: 1359 of Jiang). Jiang does not each detecting expression of said polynucleotide in a patient undergoing cancer therapy or monitoring the progress of treatment by detecting a decrease in expression of said polynucleotide in a sample from the patient taken after commencement of therapy as compared to a sample taken prior to the commencement of therapy.

However, Jiang does teach that expression levels should be monitored over time and that an increase in the level of expression indicates that the cancer is progressing,

whereas no change or a decrease indicates that the cancer is not progressing (para [01430].

Further, Mack teaches methods for monitoring treatment of a patient with cancer comprising administering a cancer treatment to the patient and determining the expression level of a gene diagnostic of cancer (see, e.g., para [0012] and [0024-0025]). Mack further teaches methods for evaluating and confirming diagnosis and treatment outcomes, including treatment outcomes of chemotherapy, comprising comparing the level of expression in a sample from the patient after treatment with a sample from the patient prior to treatment, wherein a change (decrease) in the level of expression of a target gene is detected and indicates progress of treatment and success of treatment (para [0024-0025], [0105-016]).

In view of the teachings of Mack, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Jiang so as to have detected expression of the polynucleotide of Jiang in patients prior to therapy and after the onset of therapy, including the therapy of chemotherapy, in order to have ascertained if there was a decrease in expression following therapy in order to have provided an effective means for monitoring the effectiveness of therapy and the likelihood of success of therapy.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634